

s E2a

L3 442 E2A

=> s l1 and l3

L4 216 L1 AND L3

=> s E1

L5 1 "PAU LOUIS FRANCAIS"/IN

=> s (human embryonic retinoblast?)

248743 HUMAN  
8262 EMBRYONIC  
1265 RETINOBLAST?

L6 8 (HUMAN EMBRYONIC RETINOBLAST?)  
(HUMAN (W) EMBRYONIC (W) RETINOBLAST?)

=> s l6 and l4

L7 5 L6 AND L4

=> d l7 1-5 ab bib

L7 ANSWER 1 OF 5 USPATFULL

AB Presented are ways to address the problem of replication competent **adenovirus** in adenoviral production for use with, for example, gene therapy. Packaging cells having no overlapping sequences with a selected vector and are suited for large scale production of recombinant adenoviruses. A method of the invention produces **adenovirus** incapable of replicating. The method includes a primary cell containing a nucleic acid based on or derived from **adenovirus** and an isolated recombinant nucleic acid molecule for transfer into the primary cell. The isolated recombinant nucleic acid molecule is based on or derived from an **adenovirus**, and further has at least one functional encapsidating signal, and at least one functional Inverted Terminal Repeat. The isolated recombinant nucleic acid molecule lacks overlapping sequences with the nucleic acid of the cell. Otherwise, the overlapping sequences would enable homologous recombination leading to replication competent **adenovirus** in the primary cell into which the isolated recombinant nucleic acid molecule is to be transferred.

AN 2001:185090 USPATFULL

TI Packaging systems for human recombinant **adenovirus** to be used in gene therapy

IN Fallaux, Frits Jacobus, Leiderdorp, Netherlands  
Hoeben, Robert Cornelis, Leiden, Netherlands  
Van Der Eb, Alex Jan, Oegstgeest, Netherlands  
Bout, Abraham, Moerkapelle, Netherlands  
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PI US 6306652 B1 20011023

AI US 1999-333820 19990615 (9)

RLI Continuation of Ser. No. US 1997-793170, filed on 25 Mar 1997, now patented, Pat. No. US 5994128 Continuation of Ser. No. WO 1996-NL244, filed on 14 Jun 1996  
PRAI EP 1995-201611 19950615  
EP 1995-201728 19950626  
DT Utility  
FS GRANTED  
EXNAM Primary Examiner: Priebe, Scott D.; Assistant Examiner: Nguyen, Dave Trong  
LREP Trask, Britt & Rossa  
CLMN Number of Claims: 14  
ECL Exemplary Claim: 1  
DRWN 28 Drawing Figure(s); 27 Drawing Page(s)  
LN.CNT 1883  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 2 OF 5 USPATFULL

AB The problem of replication competent **adenovirus** in virus production is solved in that we have developed packaging cells that have  
no overlapping sequences with a new basic vector and, thus, are suited for safe large scale production of recombinant adenoviruses. One of the additional problems associated with the use of recombinant **adenovirus** vectors is the host-defense reaction against treatment with **adenovirus**. Another aspect of the invention involves screening recombinant **adenovirus** vector lots, especially those intended for clinical use, for the presence of **adenovirus** E1 sequences, as this will reveal replication competent **adenovirus**, as well as revertant E1 adenoviruses. It is also an aspect of the present invention to molecularly characterize the revertants that are generated in the newer helper/vector combinations.

AN 2001:116818 USPATFULL

TI Packaging systems for human recombinant **adenovirus** to be used in gene therapy

IN Fallaux, Frits J., Leiderdorp, Netherlands  
Hoeben, Robert C., Leiden, Netherlands  
Bout, Abraham, Moerkapelle, Netherlands  
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van der Eb, Alex J., Oegstgeest, Netherlands  
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PI US 6265212 B1 20010724

AI US 1999-356575 19990719 (9)

RLI Continuation-in-part of Ser. No. US 1997-793170, filed on 25 Mar 1997, now patented, Pat. No. US 5994128

PRAI EP 1995-201611 19950615

EP 1995-201728 19950626

DT Utility

FS GRANTED

EXNAM Primary Examiner: Clark, Deborah J. R.; Assistant Examiner: Wilson, Michael C.

LREP Trask Britt

CLMN Number of Claims: 5

ECL Exemplary Claim: 1

DRWN 21 Drawing Figure(s); 20 Drawing Page(s)

LN.CNT 2294

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 3 OF 5 USPATFULL

AB A method for intracellular amplification of DNA is disclosed. The method

includes providing a mammalian cell with a first nucleic acid sequence encoding functional adenoviral **E2A** and E2B gene products and with a second nucleic acid sequence encoding a linear DNA fragment to be

amplified. The second nucleic acid sequence further has at least one functional adenoviral Inverted Terminal Repeat on a terminus and, in one embodiment where there is only a single ITR, a hairpin-like structure on the other terminus. This allows the linear DNA fragment to be acted upon by the adenoviral **E2A** and E2B gene products, thus intracellularly amplifying the linear DNA fragment, which can be extracted.

AN 2001:78920 USPATFULL  
TI Method for intracellular DNA amplification  
IN Hoeben, Robert Cornelis, Leiden, Netherlands  
Bout, Abraham, Moerkapelle, Netherlands  
PA Introgene B.V., Leiden, Netherlands (non-U.S. corporation)  
PI US 6238893 B1 20010529  
AI US 1999-334765 19990616 (9)  
RLI Continuation of Ser. No. US 793170, now patented, Pat. No. US 5994128  
PRAI EP 1995-201611 19950615  
EP 1995-201728 19950626  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Schwartzman, Robert A.  
LREP Trask Britt  
CLMN Number of Claims: 4  
ECL Exemplary Claim: 1  
DRWN 28 Drawing Figure(s); 27 Drawing Page(s)  
LN.CNT 1908  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 4 OF 5 USPATFULL

AB The invention provides improved methods and products based on adenoviral materials which can advantageously be used in for instance gene therapy.

In one aspect an adenoviral vector is provided which has no overlap with

a suitable packaging cell line which is another aspect of invention. This combination excludes the possibility of homologous recombination, thereby excluding the possibility of the formation of replication competent **adenovirus**. In another aspect an **adenovirus** based helper construct which by its size is incapable of being encapsidated. This helper virus can be transferred into any suitable host cell making it a packaging cell. Further a number of useful mutations to adenoviral based materials and combinations of such mutations are disclosed, which all have in common the safety of the methods and the products, in particular avoiding the production of replication competent **adenovirus** and/or interference with the immune system. Further a method of intracellular amplification is provided.

AN 2000:27804 USPATFULL  
TI Packaging systems for human recombinant **adenovirus** to be used in gene therapy  
IN Bout, Abraham, Ar Moerkapelle, Netherlands  
Hoeben, Robert Cornelis, Ex Leiden, Netherlands  
PA IntroGene, b.v., Netherlands (non-U.S. corporation)  
PI US 6033908 20000307  
AI US 1997-892873 19970715 (8)  
RLI Continuation of Ser. No. US 793170  
PRAI EP 1995-201611 19950615  
EP 1995-201728 19950626  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Campell, Bruce R.; Assistant Examiner: Nguyen, Dave Trong

LREP Rae-Venter Law Group, P.C.  
CLMN Number of Claims: 14  
ECL Exemplary Claim: 1  
DRWN 28 Drawing Figure(s); 27 Drawing Page(s)  
LN.CNT 2015  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 5 OF 5 USPATFULL

AB Presented are ways to address the problem of replication competent **adenovirus** in adenoviral production for use with, for example, gene therapy. Packaging cells having no overlapping sequences with a selected vector and are suited for large scale production of recombinant adenoviruses. A system for use with the invention produces **adenovirus** incapable of replicating. The system includes a primary cell containing a nucleic acid based on or derived from **adenovirus** and an isolated recombinant nucleic acid molecule for transfer into the primary cell. The isolated recombinant nucleic acid molecule is based on or derived from an **adenovirus**, and further has at least one functional encapsidating signal, and at least one functional Inverted Terminal Repeat. The isolated recombinant nucleic acid molecule lacks overlapping sequences with the nucleic acid of the cell. Otherwise, the overlapping sequences would enable homologous recombination leading to replication competent **adenovirus** in the primary cell into which the isolated recombinant nucleic acid molecule is to be transferred.

AN 1999:155512 USPATFULL

TI Packaging systems for human recombinant **adenovirus** to be used in gene therapy

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Hoeben, Robert Cornelis, Ex Leiden, Netherlands  
Van der Eb, Alex Jan, Tw Oegstgeest, Netherlands  
Bout, Abraham, Ar Moerkapelle, Netherlands  
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PI US ~~5994128~~ 19991130  
WO 9700326 19970103

AI US 1997-793170 19970325 (8)  
WO 1996-NL244 19960614  
19970325 PCT 371 date  
19970325 PCT 102(e) date

PRAI EP 1995-201611 19950615  
EP 1995-201728 19950626

DT Utility

FS Granted

EXNAM Primary Examiner: Campell, Bruce R.; Assistant Examiner: Nguyen, Dave Trong

LREP Trask, Britt & Rossa

CLMN Number of Claims: 20

ECL Exemplary Claim: 1

DRWN 21 Drawing Figure(s); 27 Drawing Page(s)

LN.CNT 2109

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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=> s E1

L8                   0 "PAU LOUIS FRANCAIS"/IN

=> s 17

5046493 HUMAN

92192 EMBRYONIC

7849 RETINOBLAST?

3 (HUMAN EMBRYONIC RETINOBLAST?)

.(HUMAN(W) EMBRYONIC(W) RETINOBLAST?)

22571 ADENOVIRUS

600 E2A

L9                   0 L6 AND L4